

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/SE 2005/000234

## A. CLASSIFICATION OF SUBJECT MATTER

IPC7: G01N 33/68

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: G01N, C12Q

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-INTERNAL, WPI DATA, PAJ

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 20020192665 A1 (ZOGHBI ET AL), 19 December 2002 (19.12.2002), [0088],[0221]-[0223],[0229],[0300], [0316]	1-8
	--	
P,Y	US 20050019801 A1 (RUBIN ET AL), 27 January 2005 (27.01.2005), [0129]-[0131],[0135]-[0136],[0140], [0434]-[0435]	1-8
	--	
Y	GAZIT ROI ET AL, "Math1 controls cerebellar granule cell differentiation by regulating multiple components of the Notch signaling pathway", Development February 24, 2004, Vol. 131, p. 903-913, pages 903-904, 911-912	1-8
	--	

☒ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

\* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"I" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

7 June 2005

Date of mailing of the international search report

08-06-2005

Name and mailing address of the ISA/

Swedish Patent Office  
Box 5055, S-102 42 STOCKHOLM

Facsimile No. +46 8 666 02 86

Authorized officer

Ida Christensen/ELY

Telephone No. +46 8 782 25 00

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 2005/000234

## C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>ZINE AZEL ET AL, "Notch/Notch ligands and Math1 expression patterns in the organ of Corti of wild-type and Hes1 and Hes5 mutant mice", Hearing Research 2002, Vol. 170, p. 22-31, ISSN:0378-5955, page 28, column 2, paragraph 2 - page 29, column 1, paragraph 1, page 30, column 1, paragraphs 1-3</p> <p>--</p>	1-8
A	<p>YANG QI ET AL, "Requirement of Math1 for Secretory Cell Lineage Commitment in the Mouse Intestine", SCIENCE, December 7, 2001, Vol. 294, p. 2155-2158, page 2157-2158</p> <p>--</p> <p>-----</p>	1-8

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 2005/000234

US	20020192665	A1	19/12/2002	AU	2002360790	A	00/00/0000
				WO	03047532	A	12/06/2003
				US	6838444	B	04/01/2005
				US	20040231009	A	18/11/2004
				US	20040237127	A	25/11/2004
				AU	5595900	A	18/12/2000
				CA	2375106	A	07/12/2000
				EP	1471926	A	03/11/2004
				JP	2003530817	T	21/10/2003
				WO	0073764	A	07/12/2000

---

US	20050019801	A1	27/01/2005	WO	2005010524	A	03/02/2005
----	-------------	----	------------	----	------------	---	------------

---

# PATENT COOPERATION TREATY

# PCT

## INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44bis)

Applicant's or agent's file reference 101317-1 WO	<b>FOR FURTHER ACTION</b>	See item 4 below
International application No. PCT/SE2005/000234	International filing date ( <i>day/month/year</i> ) 21 February 2005 (21.02.2005)	Priority date ( <i>day/month/year</i> ) 25 February 2004 (25.02.2004)
International Patent Classification (8th edition unless older edition indicated) See relevant information in Form PCT/ISA/237		
Applicant ASTRAZENECA AB		

1. This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 *bis*.1(a).
  2. This REPORT consists of a total of 7 sheets, including this cover sheet.
- In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.

3. This report contains indications relating to the following items:
 

<input checked="" type="checkbox"/>	Box No. I	°	Basis of the report
<input checked="" type="checkbox"/>	Box No. II		Priority
<input type="checkbox"/>	Box No. III		Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
<input type="checkbox"/>	Box No. IV		Lack of unity of invention
<input checked="" type="checkbox"/>	Box No. V		Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
<input checked="" type="checkbox"/>	Box No. VI		Certain documents cited
<input type="checkbox"/>	Box No. VII		Certain defects in the international application
<input type="checkbox"/>	Box No. VIII		Certain observations on the international application
4. The International Bureau will communicate this report to designated Offices in accordance with Rules 44bis.3(c) and 93bis.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44bis .2).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland  Facsimile No. +41 22 338 82 70	<table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td style="padding: 5px;">Date of issuance of this report 29 August 2006 (29.08.2006)</td> </tr> <tr> <td style="padding: 5px;">Authorized officer  Philippe Becamel  e-mail: pt12@wipo.int</td> </tr> </table>	Date of issuance of this report 29 August 2006 (29.08.2006)	Authorized officer  Philippe Becamel  e-mail: pt12@wipo.int
Date of issuance of this report 29 August 2006 (29.08.2006)			
Authorized officer  Philippe Becamel  e-mail: pt12@wipo.int			

# PATENT COOPERATION TREATY

REC'D 14 JUN 2005  
 WIPO PCT

From the  
INTERNATIONAL SEARCHING AUTHORITY

## PCT

WRITTEN OPINION OF THE  
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43bis.1)

To:

ASTRAZENECA  
Global Intellectual Property  
151 85 Södertälje  
Sweden

Date of mailing  
(day/month/year)

08 -06- 2005

Applicant's or agent's file reference

101317-1 WO

FOR FURTHER ACTION

See paragraph 2 below

International application No.

PCT/SE 2005/000234

International filing date (day/month/year)

21.02.2005

Priority date (day/month/year)

25.02.2004

International Patent Classification (IPC) or both national classification and IPC

G01N 33/68

Applicant

AstraZeneca AB et al

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☒ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

### 2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further opinions, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/SE  
Patent- och registreringsverket  
Box 5055  
S-102 42 STOCKHOLM  
Facsimile No. +46 8 667 72 88

Authorized officer

Ida Christensen/ELY

Telephone No. +46 8 782 25 00

**WRITTEN OPINION OF THE  
INTERNATIONAL SEARCHING AUTHORITY**

International application No.

PCT/SE 2005/000234

**Box No. I      Basis of this opinion**

1. With regard to the language, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.  
☐ This opinion has been established on the basis of a translation from the original language into the following language, \_\_\_\_\_, which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).
2. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
  - a. type of material  
☐ a sequence listing  
☐ table(s) related to the sequence listing
  - b. format of material  
☐ in written format  
☐ in computer readable form
  - c. time of filing/furnishing  
☐ contained in the international application as filed.  
☐ filed together with the international application in computer readable form.  
☐ furnished subsequently to this Authority for the purposes of search.
3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

WRITTEN OPINION OF THE  
INTERNATIONAL SEARCHING AUTHORITY

International application No.

PCT/SE 2005/000234

Box No. II Priority

1. ☐ The following document has not yet been furnished:

☒ copy of the earlier application whose priority has been claimed (Rules 43bis.1 and 66.7(a)).

☐ translation of the earlier application whose priority has been claimed (Rules 43bis.1 and 66.7(b)).

Consequently it has not been possible to consider the validity of the priority claim. This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43bis.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

Since it is assumed that the relevant date is the claimed priority date, the following document cited in the International Search Report will not be considered in Box V:  
US2005019801

WRITTEN OPINION OF THE  
INTERNATIONAL SEARCHING AUTHORITY

International application No.

PCT/SE 2005/000234

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1-8	YES
	Claims		NO
Inventive step (IS)	Claims		YES
	Claims	1-8	NO
Industrial applicability (IA)	Claims	1-8	YES
	Claims		NO

2. Citations and explanations:

The present application relates to a method for identifying a compound capable of modulating the Notch pathway. The test compound is either administered to an animal or is brought into contact with a cell in culture, after which the expression of the basic helix-loop-helix transcription factor Math1 in a sample from said animal or cell is detected. A change in Math1 expression in the presence of said test compound as compared to in the absence of said compound indicates that said compound modulates the Notch pathway.

Reference will be made to the following documents cited in the International Search Report:

D1) US2002192665

D2) Development, 131: 903-913 (24 Feb 2004), Gazit R et al.

From D1 it is known that the MATH1 protein regulates the Delta-Notch signalling pathway that governs endocrine cell differentiation (paragraphs [0088] and [0316]). D1 discloses an animal in which at least one Math1 allele is inactivated by insertion of a heterologous reporter gene sequence, whereby expression of Math1 is prevented. Said animal may be used in a screening assay for identifying compounds capable of affecting a developmental and/or gastrointestinal condition, wherein said condition is a result of a reduction in expression of Math1. The expression of the reporter gene is regulated by the Math1 promoter. Compounds which give a dose-related enhancement of reporter gene transcription or expression are selected for further evaluation as therapeutic agents (paragraphs [0221]-[0223], [0229] and [0300]).

...//...



WRITTEN OPINION OF THE  
INTERNATIONAL SEARCHING AUTHORITY

International application No.

PCT/SE 2005/000234

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.  
Continuation of: BOX V

The subject-matter of claims 1-8 is novel.

Document D1 is considered to represent the closest prior art.

The method of claim 1 differs from what is disclosed in D1 in that the expression of Math1 is detected instead of the expression of reporter gene driven by the Math1 promoter.

Due to these features, a direct measurement of Math1 expression is achieved instead of an indirect measure. Consequently, with the background of D1, the problem is to design an alternative method to obtain a direct measurement of Math1 expression.

It is well known to persons skilled in the art to measure the expression of a gene or protein directly, e.g. by an immunoassay or by measuring the activity of the encoded protein. Therefore, the skilled person faced with the problem of directly measuring the expression of Math1 would simply employ the features of a screening method known in the art. Since no other technical effect than the direct measurement of Math1 has been achieved the invention defined in claim 1 is not considered to go beyond what can be expected from a person skilled in the art. Therefore, the invention defined in claim 1 lacks inventive step.

The remaining claims are considered to involve particular detail executions obvious to a person skilled in the art. Therefore, the invention according to claims 2-8 is not considered to involve an inventive step.

D2 discloses that differentiation of cerebellar granule cells depends on Math1, which acts by regulating the level of multiple components of the Notch signalling pathway. D2 thereby further emphasizes what is also disclosed in D1 about the important role of Math1 in the Notch pathway. See especially pages 903-904 and 911-912.

WRITTEN OPINION OF THE  
INTERNATIONAL SEARCHING AUTHORITY

International application No.

PCT/SE 2005/000234

Box No. VI Certain documents cited

1. Certain published documents (Rules 43bis.1 and 70.10)

Application No. Patent No.	Publication date (day/month/year)	Filing date (day/month/year)	Priority date (valid claim) (day/month/year)
US2005019801	27/01/05	04/06/04	

2. Non-written disclosures (Rules 43bis.1 and 70.9)

Kind of non-written disclosure	Date of non-written disclosure (day/month/year)	Date of written disclosure referring to non-written disclosure (day/month/year)
--------------------------------	--	---

# PATENT COOPERATION TREATY

From the  
INTERNATIONAL SEARCHING AUTHORITY

REC'D 14 JUN 2005

WIPO

PCT

## PCT

WRITTEN OPINION OF THE  
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43bis.1)

To:

ASTRAZENECA  
Global Intellectual Property  
151 85 Södertälje  
Sweden

Date of mailing  
(day/month/year)

08 -06- 2005

Applicant's or agent's file reference

101317-1 WO

FOR FURTHER ACTION

See paragraph 2 below

International application No.

PCT/SE 2005/000234

International filing date (day/month/year)

21.02.2005

Priority date (day/month/year)

25.02.2004

International Patent Classification (IPC) or both national classification and IPC

G01N 33/68

Applicant

AstraZeneca AB et al

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☒ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

### 2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further opinions, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/SE

Patent- och registreringsverket

Box 5055

S-102 42 STOCKHOLM

Facsimile No. +46 8 667 72 88

Authorized officer

Ida Christensen/ELY

Telephone No. +46 8 782 25 00

**WRITTEN OPINION OF THE  
INTERNATIONAL SEARCHING AUTHORITY**

International application No.

PCT/SE 2005/000234

**Box No. I      Basis of this opinion**

1. With regard to the language, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.  
☐ This opinion has been established on the basis of a translation from the original language into the following language, \_\_\_\_\_, which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).
2. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
  - a. type of material  
☐ a sequence listing  
☐ table(s) related to the sequence listing
  - b. format of material  
☐ in written format  
☐ in computer readable form
  - c. time of filing/furnishing  
☐ contained in the international application as filed.  
☐ filed together with the international application in computer readable form.  
☐ furnished subsequently to this Authority for the purposes of search.
3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

WRITTEN OPINION OF THE  
INTERNATIONAL SEARCHING AUTHORITY

International application No.

PCT/SE 2005/000234

Box No. II Priority

1. ☐ The following document has not yet been furnished:

☒ copy of the earlier application whose priority has been claimed (Rules 43bis.1 and 66.7(a)).

☐ translation of the earlier application whose priority has been claimed (Rules 43bis.1 and 66.7(b)).

Consequently it has not been possible to consider the validity of the priority claim. This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43bis.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

Since it is assumed that the relevant date is the claimed priority date, the following document cited in the International Search Report will not be considered in Box V:  
US2005019801

WRITTEN OPINION OF THE  
INTERNATIONAL SEARCHING AUTHORITY

International application No.

PCT/SE 2005/000234

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1-8	YES
	Claims		NO
Inventive step (IS)	Claims		YES
	Claims	1-8	NO
Industrial applicability (IA)	Claims	1-8	YES
	Claims		NO

2. Citations and explanations:

The present application relates to a method for identifying a compound capable of modulating the Notch pathway. The test compound is either administered to an animal or is brought into contact with a cell in culture, after which the expression of the basic helix-loop-helix transcription factor Math1 in a sample from said animal or cell is detected. A change in Math1 expression in the presence of said test compound as compared to in the absence of said compound indicates that said compound modulates the Notch pathway.

Reference will be made to the following documents cited in the International Search Report:

D1) US2002192665

D2) Development, 131: 903-913 (24 Feb 2004), Gazit R et al.

From D1 it is known that the MATH1 protein regulates the Delta-Notch signalling pathway that governs endocrine cell differentiation (paragraphs [0088] and [0316]). D1 discloses an animal in which at least one Math1 allele is inactivated by insertion of a heterologous reporter gene sequence, whereby expression of Math1 is prevented. Said animal may be used in a screening assay for identifying compounds capable of affecting a developmental and/or gastrointestinal condition, wherein said condition is a result of a reduction in expression of Math1. The expression of the reporter gene is regulated by the Math1 promoter. Compounds which give a dose-related enhancement of reporter gene transcription or expression are selected for further evaluation as therapeutic agents (paragraphs [0221]-[0223], [0229] and [0300]).

...//...

WRITTEN OPINION OF THE  
INTERNATIONAL SEARCHING AUTHORITY

International application No.

PCT/SE 2005/000234

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.  
Continuation of: BOX V

The subject-matter of claims 1-8 is novel.

Document D1 is considered to represent the closest prior art.

The method of claim 1 differs from what is disclosed in D1 in that the expression of Math1 is detected instead of the expression of reporter gene driven by the Math1 promoter.

Due to these features, a direct measurement of Math1 expression is achieved instead of an indirect measure. Consequently, with the background of D1, the problem is to design an alternative method to obtain a direct measurement of Math1 expression.

It is well known to persons skilled in the art to measure the expression of a gene or protein directly, e.g. by an immunoassay or by measuring the activity of the encoded protein. Therefore, the skilled person faced with the problem of directly measuring the expression of Math1 would simply employ the features of a screening method known in the art. Since no other technical effect than the direct measurement of Math1 has been achieved the invention defined in claim 1 is not considered to go beyond what can be expected from a person skilled in the art. Therefore, the invention defined in claim 1 lacks inventive step.

The remaining claims are considered to involve particular detail executions obvious to a person skilled in the art. Therefore, the invention according to claims 2-8 is not considered to involve an inventive step.

D2 discloses that differentiation of cerebellar granule cells depends on Math1, which acts by regulating the level of multiple components of the Notch signalling pathway. D2 thereby further emphasizes what is also disclosed in D1 about the important role of Math1 in the Notch pathway. See especially pages 903-904 and 911-912.

WRITTEN OPINION OF THE  
INTERNATIONAL SEARCHING AUTHORITY

International application No.

PCT/SE 2005/000234

Box No. VI Certain documents cited

1. Certain published documents (Rules 43bis.1 and 70.10)

Application No. Patent No.	Publication date (day/month/year)	Filing date (day/month/year)	Priority date (valid claim) (day/month/year)
US2005019801	27/01/05	04/06/04	

2. Non-written disclosures (Rules 43bis.1 and 70.9)

Kind of non-written disclosure	Date of non-written disclosure (day/month/year)	Date of written disclosure referring to non-written disclosure (day/month/year)
--------------------------------	--	---